PHOENIX
TRANSLATIONS

September 25, 2008

Re: International Publication Number WO 02/087557 A1

To Whom It May Concern:

This is to certify that the above-referenced document (.pdf file "106-18330_ WO02087557A1") has been translated from German into English by a professional translator on our staff who is skilled in the German language.

The attached English translation conforms essentially to the original German except for those words or phrases for which there are no equivalents. Such words or phrases are noted in the translation along with the best English meaning.

Kim Kyle

Subscribed and sworn to before me on September 25, 2008.

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My Commission Expires
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For explanation of the two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR TREATING RETINA OR PHOTORECEPTOR DEGENERATION

(57) Abstract: The invention relates to the use of a sugar for producing a preparation containing sugar for treating degenerative illnesses of the photoreceptors of vertebrates, particularly humans. The invention enables a medicament which is easy to handle and stable to be made available for the first time.

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Method for Treating Retina or Photoreceptor Degeneration

The present invention concerns use of a substance for treatment of retina or photoreceptor degeneration of the eye or other sensory cells in vertebrates, especially in humans.

It is known from the article "Neuroprotectants in Honghua: Glucose attenuates retinal ischemic damage"; Romano et al.; Invetigative Opthalmology & Visual Science, January 1993, Vol. 34, No. 1, that glucose can moderate the sequelae of retinal ischemia, i.e., deficient blood supply or oxygen supply to the retina. Retinal ischemia is a disease with a different cause than the diseases to be treated with the present invention, which are attributed to degeneration of photoreceptors, and which also occur when oxygen supply to the retina is undisturbed.

A method for treatment of diseases that are due to degeneration of photoreceptors or other vision cells, for example, in the organ of Corti or in the vestibular organ itself, as well as acquired sensory cell damage, is known from DE-19718826 A1. There it is proposed, among other things, for treatment of macular degeneration and retinitis pigmentosa, to apply substances subretinally or intravitreally, which influences the extracellular space surrounding the photoreceptors. The substances include adenosine triphosphate (ATP), which is an energy supplier, in addition to guanosine triphosphate (GTP).

For practical daily application by patients, however, storage and handling of ATP appears to be too difficult. The shelf life of ATP or ATP-containing drugs is only limited, under everyday conditions. Finally, such drugs are relatively costly. The diseases to be treated include:

- Macular degeneration or dystrophy;
- Retinitis pigmentosa;
- Usher syndrome
- Rod/cone degenerations or dystrophies
- Cone/rod degenerations or dystrophies

- Stargardt's disease
- Pattern dystrophy
- Fundus flavimaculatus
- Sorby's fundus dystrophy
- Punctus albinopunctatus
- Refsum's disease
- Choroideremia,
- Bardet-Biedle syndrome
- Leber's congenital amaurosis.

Acquired degenerations of sensory cells or epithelial cells adjacent to sensory cells, or of support cells in humans can also include the following:

- Night blindness after treatment with vincristine or vinblastine,
- Sequelae of treatment with thioridazine, chloroquine, quinine or other ototoxic substances,
- Sequelae of treatment after retinal detachment,
- Sequelae of retina infection,
- Sequelae of a deficiency of physiological sensory stimulation,
- Sequelae of age-related sensory cell degeneration,
- Sequelae of non-physiological sound load,
- Sequelae of non-physiological

head acceleration load.

It is therefore the task of the present invention to provide a use of a substance for treatment of the mentioned diseases, in which a substance is used that has simpler handling and application, as well as better storage life than ATP.

This task is solved by a use with the features of Claim 1.

Because a sugar (monosaccharide, disaccharide or polysaccharide) is used, especially intraocularly administered glucose, an energy source is made available to the photoreceptor cells in their immediate surroundings, which can moderate or eliminate an energy deficiency of the photoreceptors. The energy deficiency is indirectly or directly responsible for degeneration of photoreceptor cells. Sugar can be the sole active ingredient, or can be used in an active ingredient combination.

D-glucose is preferably applied.

The preparation can be applied as a liquid or solid, the latter for example in the form of implanted pellets. A concentration of glucose, applicable in liquid preparations, preferably lies in the range from 10 mmol D-glucose solution, in which the glucose is contained in an appropriate carrier solution. Application preferably occurs subretinally or intravitreally.

With intraocular application of glucose, the energy balance of the photoreceptors disturbed during degenerative diseases of the photoreceptors, especially in retinitis pigmentosa and macular degeneration, is restored. Degeneration of photoreceptors can be slowed or stopped in this way. An already-present degeneration can also be moderated by application of glucose.

It can also be prescribed to use lactose, fructose, sucrose or glycogen. Intraocular application can also occur via an active ingredient depot arranged on or in the eye.

The probable cell biological basis for the additional energy demand of photoreceptors is initially explained below, and then the method of action of glucose is explained in the area of photoreceptors.

The photoreceptor cells of mammals, like those of humans, respond when light is absorbed by the pigment molecules in the outer segments, which triggers a series of biochemical reactions. These biochemical reactions are called phototransduction. Without the further effect of light, these reactions stop after a certain time and the outer segments return to their original state, the dark-adapted state, so that they can absorb light again.

Photoreceptors can function over a very large range of surrounding brightness, because they can adapt to a given brightness level. The adaptation of light sensitivity probably occurs via a change in calcium concentration in the cytoplasm of the outer segments. The size of the impulse response to incident light is also adapted, for example, by a controlled and adapted change of an amplification factor that states the signal per absorbed photon. The amplification factor is high at a low brightness level; at high brightness, the amplification factor is low.

The retina of vertebrates can respond to very limited brightness, as occurs for example at night in moonlight. The very sensitive rod-shaped photoreceptors are used in this case. With greater ambient brightness (sunshine), cone-like photoreceptors are used. In a small area of medium brightness, which roughly corresponds to dusk, both rods and cones are used. In the natural world, before the introduction of artificial lighting, night vision therefore occurred via the sensitive rods, whereas daytime vision was provided by the cones, while the rods are in the light-adapted state and are saturated with respect to light sensitivity.

Many of the proteins, whose gene defects in humans produce degeneration of photoreceptors, are proteins that occur in the outer segments of the photoreceptors and participate in phototransduction. It is therefore assumed that these proteins play a role in the amplification factor of phototransduction or are influenced by this amplification factor.

Rods are much more sensitive to degeneration phenomena than cones. In many diseases of the human retina, degeneration of the rods precedes degeneration of the cones.

All or almost all of these biochemical reactions (phototransduction, adaption to brightness levels) require energy. The energy demand of different reactions, however, is of different magnitude.

In the context of evolution, mechanisms were developed to avoid needless energy consumption. Thus, in many if not all retinas of mammals, a special mechanism is used to avoid unnecessary energy consumption during the roughly 12 hours of daylight, in order to decouple the outer segments of the rods from the first steps of phototransduction (light absorption by rhodopsin) from the later steps of phototransduction. This mechanism presumably means that the amplification factor of the outer segments of the rods is kept at zero. Ultimately, the rods "know" that they are not needed for about 12 hours, so that during this time they need not continuously consume unnecessary energy, in order to stop the light-induced reactions. This unnecessary energy would be used for the rods to attempt to achieve dark adaption if daylight fails, which does not occur except during a solar eclipse.

The outer segments of the photoreceptors have a cytoskeleton, based on supporting microtubules (small, elongated, solid intracellular structures), to which certain protein molecules within the membrane are fastened by fiber-like bonds. Because of the biochemical identity of many of these proteins, which are arranged in the cytoskeletal systems, these are at least sometimes the intracellular locations, at which control and regulation of the amplification factor of the outer segments of the cone and rod photoreceptors occurs, and where the decoupling mechanism of the outer rod segments consequently occurs.

The outer segments of all rods and cones have a cytoskeletal system containing such microtubuli (the axons of the cilium), which is very similar in both cell types and participates in control and regulation of the amplification factor of the outer segments. The outer segments of the rods however, in many retinas for example, in humans and in amphibians, have an additional cytoskeletal system on their multiple constrictions, which is separated from the cytoskeletal

system of the cilium and differs from it. This rod-specific cytoskeletal system on the multiple constrictions of the outer rod segments in the retina of humans is probably the location of the mechanism for decoupling of phototransduction of the rods during daylight, specific to the rods, in order to avoid an undersupply of energy. Many human photoreceptor degenerations are due to a defect of this cytoskeletal system.

Degeneration of rod-like photoreceptors, which is accompanied by failure of the cytoskeletal system specific to the rods, is due to the incapability of the rods of transferring to the light-insensitive state (amplification factor close to zero) or remaining in this state. Since the energy-saving state is not reached, energy is required in excess, which is not available in the otherwise undisturbed system. The energy deficiency resulting from this is ultimately the direct cause for the damage that occurs on rod photoreceptors. Similarly, the cytoskeleton of the cilium participates in regulation of the amplification factor in the rods and cones, so that a gene defect in this system can lead to a defective mechanism, and also to increased energy demand.

Supply of energy to the retina of mammals, especially humans, more precisely to the photoreceptors of the human retina, therefore causes prevention or moderation of degeneration of the photoreceptors. In this way amaurosis due to these degeneration phenomena can be prevented or at least significantly delayed.

The use of glucose, according to the invention for intraocular application, provides a large degree of practical handling capability, relative to known methods. Glucose is a known, biochemically stable and inexpensive drug, whose handling is uncomplicated, and which is also very durable with respect to storage and transport. These advantages are an important criterion for the success of continuously required treatments, which is supposed to be conducted without considerable equipment expense, and without demanding training of medical personnel.

Glucose is also simple to use, and reliable in implantable application and dosing systems, relative to other known substances. The same advantages are obtained, if a preparation based on glucose is used for treatment of hereditary or acquired sensory cell degenerations in the inner ear, in the organ of Corti or in the vestibular organ.

Finally, a major advantage of glucose is the fact that it is a substance with excellent physiological compatibility, which also occurs in the natural extracellular environment of photoreceptors and other sensory cells.

Claims

1. Use of a sugar to product a sugar-containing preparation for treatment of degenerative diseases of photoreceptors and other sensory cells of vertebrates, especially humans.

2. Use according to Claim 1, **characterized by the fact** that the sugar is D-glucose.

3. Use according to one of the preceding claims, **characterized by the fact** that treatment occurs by intraocular, especially intravitreal of subretinal, application or extraocular application of the preparation as a liquid.

4. Use according to one of the preceding claims, **characterized by the fact** that treatment occurs by intraocular, especially intravitreal or subretinal application or extraocular application of the preparation as a solid.

5. Use according to one of the preceding claims, **characterized by the fact** that the preparation has glucose in a concentration of 5 mmol to 20 mmol, especially 10 mmol.

6. Use according to one of the preceding claims, **characterized by the fact** that the disease being treated is chosen from the group comprising the following diseases:
   - Macular degeneration or dystrophy;
   - Retinitis pigmentosa;
   - Usher syndrome
   - Rod/cone degenerations or dystrophies

- Cone/rod degenerations or dystrophies
- Stargardt's disease
- Pattern dystrophy
- Fundus flavimaculatus
- Sorby's fundus dystrophy
- Punctus albinopunctatus
- Refsum's disease
- Choroideremia,
- Bardet-Biedl syndrome
- Leber's congenital amaurosis.

7. Use according to one of the preceding Claims 1 to 5, **characterized by the fact** that the acquired degenerations of sensory cells or epithelial cells, glia cells or support cells adjacent to sensory cells in humans include the following:
   - Night blindness after treatment with vincristine or vinblastine,
   - Sequelae of treatment with thioridazine, chloroquine, quinine or other ototoxic substances,
   - Sequelae of treatment after retinal detachment,
   - Sequelae of retina infection,
   - Sequelae of a deficiency of physiological sensory stimulation,
   - Sequelae of age-related sensory cell degeneration,
   - Sequelae of non-physiological sound load,
   - Sequelae of non-physiological

   head acceleration load.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7004 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 628 314 A (SENJU PHARMACEUTICAL) 14 December 1994 (1994-12-14) claims 1-3 page 2, line 46-52	1-5
X	FR 2 734 159 A (NICOLAS FRANÇOIS MICHEL) 22 November 1996 (1996-11-22) claims 1,3 page 1, line 20-33	1,3,4,6
X	EP 0 799 615 A (TAISHO PHARMACEUTICAL) 8 October 1997 (1997-10-08) claims 1,3 page 2, line 9-12	1-3,5,7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	C.ROMANO E.A.: "Intravitreal injection of glucose protects against ischemic degeneration of retinal neurons" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 17, no. 1-2, 1991, page 1078 XP001064541 page 1078, paragraph 425.3 -----	1-3,6,7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int nal Application No
PCT/EP 01/04867

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 628314	A	14-12-1994	AU	675304 B2	30-01-1997
			AU	6337294 A	08-12-1994
			CA	2125056 A1	05-12-1994
			EP	0628314 A1	14-12-1994
			JP	7048262 A	21-02-1995
			KR	143509 B1	15-07-1998
FR 2734159	A	22-11-1996	FR	2734159 A1	22-11-1996
EP 799615	A	08-10-1997	AT	202930 T	15-07-2001
			AU	695322 B2	13-08-1998
			AU	4189696 A	10-07-1996
			DE	69521717 D1	16-08-2001
			DE	69521717 T2	31-10-2001
			EP	0799615 A1	08-10-1997
			US	5945121 A	31-08-1999
			CA	2205863 A1	27-06-1996
			CN	1170364 A	14-01-1998
			WO	9619211 A1	27-06-1996

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